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New Concepts of Digitalis

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■ *The data presented in this review have substantiated the following ideas:*

• *There is a direct relationship between digitalis dosage and myocardial contractile force. A small dose of digitalis produces a small increase of the contractile force of the heart and a large dose increases the force of the heart's contraction by a much greater amount, whether the heart is normal, has a poor reserve, or is in frank failure.*

• *Digitalis is of benefit to the patient with cardiovascular disease whether his heart is in failure or not.*

DIGITALIS HAS BEEN RESERVED in the past to slow the pulse of a patient with a rapid ventricular response during atrial fibrillation or flutter, and to aid the heart that is in frank failure. Frequently an attempt has been made to administer a "full digitalizing dose" since there has been a belief that a dose smaller than that is not effective. Over the past decade or two a body of data has been accumulating, in the laboratory and at the bedside, which has extended the use of digitalis. It has been demonstrated that digitalis, even in low dose, increases the ability of the heart to pump out the blood that comes to it. This effect of digitalis is produced in the normal heart, as well as the heart with pathologic changes but not in failure, and also in the heart which has failed. This paper is a review of the literature with the aim of supporting two ideas about digitalis. The first idea is that there is a direct relationship between digitalis dosage and contractile force of the heart; and the second is that digitalis is of benefit to the patient with heart disease but not in frank heart failure.

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Relationship Between Digitalis Dose And Contractile Force of Heart

The idea that a "full digitalizing dose" of a cardiac glycoside must be given to achieve any effect on the myocardium has probably come from the observation that large doses of digitalis must be given to slow the ventricular response of the heart

during atrial fibrillation and flutter. However, that which holds true for the conduction effect of digitalis does not necessarily apply to the inotropic effect of the drug. Starr[1] summarized his views on the dose of digitalis after reviewing his studies with the ballistocardiograph in patients: "The idea of the digitalizing dose, the conception that a certain amount of digitalis, calculated from the patient's weight, had to be given before there was *any* digitalis action has proved wrong. This idea was based on observations made on heart rate. Measuring the forces, one finds that much smaller doses than this have definite effects on the heart's performance in many patients, often in the absence of changes of rate."

An instrument has been developed, the strain gauge, which can be sutured onto the ventricle of the heart to measure the force of the muscular contraction. This device makes it possible to assess the increase of the force of ventricular contraction produced by digitalis. In 1950, Walton et al[2] sutured a strain gauge to the right ventricle of normal dogs and found a direct relationship between the dose of all cardioactive drugs tested and an increase of contractile force of the heart. They found with ouabain that 0.25 of a cat unit increased the contractile force 25 percent above normal, 0.75 of a cat unit raised the contractile force 65 percent above normal and 1.25 cat units raised the contractile force 100 percent above normal. They stated: "The electrocardiograms did not show distinctive changes before development of substantial increases in contractile force. In a few instances, maximal contractile force changes preceded by a distinct interval any significant manifestation of the typical ECG changes."

Williams et al,[3] in 1966, studied the contractile force of the right ventricle in normal dogs and found that 60 percent of the toxic dose of ouabain raised the contractile force 43 percent above the control level, 80 percent of the toxic dose raised the contractile force 48 percent above normal, the toxic dose raised the ventricular contractile force 65 percent above normal, and when the arrhythmia was controlled with intravenous potassium, and more ouabain was given, the contractile force rose to 84 percent above normal.

An increase of contractile force of the ventricle causes the heart to empty more rapidly. The decrease of emptying time can be used as a measure of the effect of a given dose of digitalis on the contractile force of the heart. Weissler et al,[4] in 1965, studied 30 normal college males and measured the total duration of left ventricular systole from the onset of ventricular depolarization to the closure of the aortic valves by simultaneously recording the electrocardiogram and the phonocardiogram. Eight hours after an intravenous dose of deslanoside, they found that the emptying time had been shortened 14 milliseconds by the action of 0.4 mg of the drug, 20 milliseconds by 0.8 mg and 34 milliseconds by a 1.6 mg. They summarized their findings: "The mean response in the duration of each of the phases of systole during the first eight hours following administration of deslanoside proved to be dose-dependent."

Less than a "digitalizing dose" of lanatoside-C (Cedilanid®), 0.8 mg, has been shown to be effective in improving the cardiac status of patients with damaged hearts. Lagerlof and Werko,[5] in 1949, administered such a dose to five patients who were in failure. They measured the cardiac output before and after digitalization and found: "The cardiac output invariably rose in the cases in heart failure while the response in the other cases sometimes was in the direction of increase, sometimes in the direction of decrease."

Malmcrona et al,[6] in 1966, gave 0.8 mg of lanatoside-C (Cedilanid®) to ten patients who had acute myocardial infarction and a substantial fall in arterial pressure but without left ventricular failure or cardiogenic shock. They found a rise in blood pressure after the administration of the digitalis and summarized their findings: "This study indicates that a moderate digitalis dose, given intravenously to patients with myocardial infarction, may be beneficial rather than dangerous, even in the absence of overt failure, as judged from the hemodynamic effects."

It can be deduced from these studies that one of the physiological effects resulting from the administration of digitalis, an increase in contractile force of the ventricle, is dose-dependent: a small dose of the drug produces a small increase of the contractile force and a large dose results in a large increase in the contractile force of the ventricle.

Beneficial Effect of Digitalis To the Heart Not in Failure

General Considerations

Digitalis has been shown to increase the cardiac output of the heart in failure and also has been

shown to decrease the cardiac output of the heart which is not in failure.[7,8] It was therefore assumed that digitalis was beneficial to the heart in failure and detrimental to the heart not in failure. This was an erroneous assumption regarding the heart not in failure since the fall in cardiac output is probably due to a peripheral vascular constriction that digitalis produces.[8,9] Such vascular constriction can result in a diminished venous return to the heart and also an increased resistance to the arterial outflow.

There has been considerable experimental work in animals and observation in humans demonstrating that digitalis increases the contractile force of the heart whether it is normal, abnormal but not in failure, or in frank failure. This increase in contractile force has been demonstrated to be beneficial to the chronically stressed heart, as well as to the heart with poor reserve.

Cotten and Stopp,[10] in 1958, demonstrated that digitalis increases the ability of the normal heart to pump out the blood that comes to it. They studied the effect of digitalis in normal dogs by measuring the myocardial contractile force and also by progressively increasing the left atrial pressure and measuring the stroke work as the heart load increased. They summarized their findings: "The increase in left ventricular contractile force provoked by ouabain and the higher ventricular function curves obtained after injection of this glycoside show conclusively that ouabain stimulates the non-failing heart of the dog with a complete circulatory system."

Stewart et al,[11] in 1938, studied 13 patients with compensated heart disease by digitalizing them over 24 hours and recording their cardiac output, electrocardiograms and heart size. They concluded that the factor common to all patients as a result of digitalis was an increase of work per beat.

Sokolow et al,[12] in 1942, studied four patients who had been in failure and were being maintained with digitalis. Discontinuing digitalis allowed them to go into failure again. To evaluate failure, these investigators used the vital capacity measurement, venous pressure, hepato-jugular reflux, circulation time, weight and clinical evaluation. They stated: "Continuous digitalization is of value in preventing recurrences of cardiac failure in ambulatory patients with sinus rhythm. It is unwise to omit this drug in patients with diminished cardiac reserve who have previously shown failure, even though the patient is free of symptoms."

Erickson and Fahr,[13] in 1945, studied 39 patients who had no evidence of failure but had enlarged hearts and a slowed circulation time. They found that digitalization improved the mechanical efficiency of the hearts of 87 percent of the patients studied. "We believe," they said, "that digitalis is definitely indicated for organically diseased and enlarged hearts which appear compensated, when the circulation time, as measured by the calcium gluconate arm-to-mouth method, is greater than 16 seconds."

Hedlund,[14] in 1952, studied 12 patients with latent cardiac insufficiency (no overt failure) using an exercise test with determination of oxygen consumption and oxygen debt. He found that digitalization effectively decreased the oxygen consumption during work and also decreased the relative oxygen debt. He summarized, in an abstract to the author: "Therefore, it is expedient not to suspend glycoside therapy, even when the patient is in good clinical condition and is compensated. As in the case of cardiac decompensation, the patient should receive an uninterrupted treatment with the cardiac glycosides."

Braunwald et al,[15] in 1961, studied 21 patients with heart disease, who were not in failure, by suturing strain gauges to their right ventricles. They found that acetyl strophanthidin increased the contractile force an average of 87 percent above control and Cedilanid® increased the contractile force 31 percent. They summarized their views: "In view of the positive inotropic effect of digitalis on the non-failing heart, the fear of cardiac depression when these drugs are used 'prophylactically' . . . would not seem to be warranted. Thus, the exhibition of cardiac glycosides does not appear to be contraindicated in patients without overt heart failure in whom the development of heart failure is feared because of the superimposition of an excessive hemodynamic burden resulting from an acute infection or surgical procedure. Indeed, the demonstration in the present study of the substantial augmentation of contractile force provided by digitalis has led to the establishment of a policy at the National Heart Institute to digitalize all patients prior to intracardiac surgery."

Selzer and Malmborg,[16] in 1962, studied 15 patients who had been in left heart failure and were relieved of their frank failure by bed rest, diuretics and low salt. They recorded the patients'

cardiac pressures and performance under exercise. They observed the results before digitalization: "In all patients, the abnormal circulatory dynamics were accentuated by exercise, as evidenced by the further rise in left atrial and pulmonary arterial pressure, and an inadequate increase in cardiac output." Also they summarized the results after digitalization: "Ten patients showed significant improvement consisting of lowering left atrial and pulmonary arterial pressures and an average increase in resting cardiac output of 40 percent. Five patients showed no significant hemodynamic change."

Kahler et al,[17] in 1963, studied the oxygen debt that three compensated cardiac patients developed from exercise during the time that they were not receiving digitalis, when they were receiving digitalis, and when they were receiving placebos, in various sequence. "All had inactive rheumatic valvular disease, cardiomegaly, and a history of cardiac decompensation some months or years previously, but had none of the clinical signs of congestive heart failure at the time of the study. These three patients were selected because they were capable of performing light physical activities without cardiac symptoms in the absence of digitalis therapy." The authors summarized their findings and opinions: "In all patients the oxygen debt was smaller during the period of digoxin administration, although the external work performed was identical. . . . The accumulation of a smaller oxygen debt following exercise while these subjects were receiving digoxin indicates that the functional status of their circulatory system was improved by the drug. . . . It would appear that digitalis administration is beneficial to at least some patients who have cardiac disease and enlarged hearts and some decrease in cardiac reserve without signs or symptoms of heart failure."

Mason and Braunwald,[18] in 1963, studied ten patients when they were not digitalized and when they were digitalized. They found that digitalis increased the myocardial contractile force in those unanesthetized humans with a normal heart and those with an abnormal heart that was not in failure. They studied the rate of change of the intraventricular pressure which is an index of the contractile force of the heart. They summarized their findings: "In four patients without heart disease and in two patients with minimal cardiac abnormalities and normal right ventricular function, 0.30 to 0.60 mg ouabain elevated the right ventricular peak rate of change (dp/dt) by 9.9 to 73.5 percent (average = 31.5 percent of control values). In four patients with uncomplicated atrial septal defects, in whom the left ventricular hemodynamic burden and left ventricular function were normal, 0.60 mg oubain elevated the left ventricular peak dp/dt by 26.3 to 48.8 percent (average = 35.5 percent) of control value. These observations in intact, unanesthetized subjects indicate that ouabain is capable of stimulating the contractility of the non-failing and of the normal human heart."

Murphy et al, [19] in 1964, studied nine patients with cardiac disease by catheterizing the right and left (transseptal) sides of the heart. Three of the patients were in heart failure and six were compensated. Various indices were studied before and after digitalization—cardiac index, stroke index and stroke work, stroke power, mean systolic ejection rate, left ventricular end-diastolic pressure, first derivative of left ventricular systolic pressure (dp/dt), mean systolic ejection period, systemic arterial pressure and ventricular function points. They commented on their findings: "It is of clinical interest that evidence of augmented ventricular performance was found in our patients with cardiomegaly but no detectable clinical heart failure. Improvement of ventricular performance in these cases after digitalization was characterized mainly by an increase in the rate of rise of left ventricular pressure and a general tendency of ventricular function points to shift left and upward on the stroke work-left ventricular diastolic pressure diagram."

Sonnenblick et al,[20] in 1966, studied six patients who had previously had operations on the heart but were in a compensated state. Metal clips had been sutured to the ventricular surface so that cineradiographs could be taken to record the velocity of contraction and this rate was related to the force of contraction as determined by the arterial pressure. The studies were done before and after digitalization. They summarized their findings: "It was observed that ouabain always augmented myocardial contractility as reflected in the force-velocity relation. Velocity of shortening increased an average of 77 ±5 (SEM) percent. . . . It is concluded that the fundamental action of digitalis glycosides is to augment the contractile state of the heart, whether normal or failing, but that in the absence of heart failure this improve-

ment is not translated into an increase in cardiac output."

Reindell and Konig,[21] in 1967, reported on studies of several hundred volunteers and patients during which they determined the myocardial reserve by doing exercise tests. During the exercise tests, they measured the heart rate, the heart size and the oxygen uptake. They found that patients who were not in failure but who had fixed hypertension, coronary insufficiency or branch blocks, or who had had myocardial infarction, showed performance tests that were well below the normal for their ages. In other words, a "loading insufficiency" developed. These patients were shifted to the normal or near normal status by digitalization. These investigators summarized their studies: "According to these findings there is no doubt that the uneconomical mode of operation of the heart which becomes insufficient of loading is decisively improved due to application of digitalis. This results in the basic demand that the heart which is insufficient on loading should be digitalized in the same way as the heart which is insufficient at rest."

Mason,[22] in 1968, summarized the mode of action of digitalis: "Since digitalis has the same fundamental action on both normal and failing hearts, the view that the drug has a harmful effect on the non-failing heart cannot be given credibility. Digitalis lowers the oxygen debt following exercise in patients with cardiomegaly but without heart failure, indicating that the functional status of the circulatory system may be improved by the drug in at least some patients without overt failure. In addition, digitalis may be of potential clinical value in preventing the development of ventricular hypertrophy in patients with aortic valvular disease or hypertension without heart failure, since the drug reduces the degree of mortality from heart failure and the degree of ventricular hypertrophy resulting from a chronic pressure load in experimental animals, further, the belief that the administration of digitalis in special situations may be helpful in certain cardiac patients without failure is gaining in prevalence. Thus, prophylactic digitalization may protect the myocardium in these patients in the face of the depressing effects of anesthesia and operation, serious illnesses such as pneumonia, and the hypervolemic state during pregnancy."

The benefit of digitalis to the acutely stressed heart of the dog was shown by Selzer et al,[23] in 1953. During thoracotomy, they measured the amount of constriction that could be applied to the pulmonary artery and the length of time the constriction could be tolerated before failure occurred. The studies were done before and after ouabain was administered. They stated: "It seems reasonable to conclude from the results of this study that the group of digitalis drugs may exert a favorable effect upon the normal heart during unusual stress. It seems difficult to visualize a clinical situation where such a property of digitalis would appear useful. However, if a similar action could be demonstrated upon the competent hypertrophied heart, where such an effect could conceivably be much more useful, then earlier prophylactic use of digitalis could be justified in compensated heart disease."

In 1908 and 1929, Cloetta[24,25] found that digitalis prevented the chronically stressed rabbit heart from enlarging as much as the undigitalized stressed heart. He avulsed a single aortic valve in the animals and maintained half of the group on digitalis. At the end of one year, the untreated animals had an increase of heart size 80 percent above the normal unstressed rabbit heart and the digitalis-treated animals had only a 38 percent increase of heart size above normal. In addition, acute performance tests of the hearts were made and the results were summarized: ". . . one finds that the crippled digitalis treated heart is almost equal to the normal; while the defective heart without digitalis treatment is much more rapidly exhausted. The capacity of the former is nearly double that of the latter, a fact of great importance in practice. This should be sufficient to induce prophylactic treatment with digitalis in all early cases of endocarditis which are apt to terminate in valvular lesions."

Williams and Braunwald,[26] in 1965, studied chronic heart strain in rats by constricting the abdominal aorta, which resulted in hypertension. Some of the rats were maintained on digitalis. Their results were similar to those of Cloetta. Fewer of the digitalized rats died from heart failure and the weight gain of the digitalized hearts was less than the undigitalized hearts.

Preoperative Digitalis Benefits The Patient with Myocardial Disease

The stress of surgical operation on the myocardium is considerable with frequent occurrence of hypoxia,[27] hemorrhage, and depression from

anesthetic drugs.[28] These strains are detrimental to the patient with myocardial disease, as revealed by a high incidence of postoperative cardiac complications. Sufficient data have now been accumulated to show that preoperative digitalization protects the hearts of those patients who have cardiac disease but are not in failure.

The thoracotomy patient

Wheat and Burford,[29] in 1961, reported on a retrospective study of 439 patients who had thoracotomy. These investigators summarized their findings: "Cardiac complications following major intrathoracic resections can be reduced from 20 to 10 percent over the age of 55 by prophylactic preoperative digitalization. . . . All patients over 60 years of age in whom a major intrathoracic resection is contemplated should be digitalized routinely preoperatively."

Heilbrunn and Hardin,[30] in 1963, retrospectively reviewed 89 patients over 70 years of age who had thoracotomy. They found that non-digitalized patients had a 24 percent incidence of postoperative arrhythmia and the arrhythmia caused or contributed to the death of 4 percent of the total number of undigitalized patients. The patients who had been digitalized preoperatively had a postoperative incidence of arrhythmia of 1 percent which did not contribute to or cause fatality. Heilbrunn and Hardin summarized their results: "We believe that prophylactic digitalization is indicated in patients over 70 who undergo thoracic procedures and is of value in avoiding and controlling postoperative arrhythmias."

Bergh et al,[31] in 1967, retrospectively reviewed 229 cases of pneumonectomy, in 148 of which the patients had had prophylactic digitalization. The incidence of postoperative atrial fibrillation was 10 percent in the digitalized group and 20 percent in the non-digitalized. The patients were digitalized on the day of operation after surgery had been completed.

Burman,[32] in 1965, reported on 244 patients over the age of 40 who had major thoracic surgical procedures without extracorporal circulation. One hundred and fifty-nine of them were digitalized to the limit of tolerance and 85 were either incompletely digitalized or not digitalized at all. The incidence of arrhythmias or congestive failure that occurred during the first three weeks postoperatively in the fully digitalized group was 3.2 percent and in the other group was 16.4 percent. The mortality from cardiac complication in the fully digitalized group was 1.3 percent and in the other group was 7 percent. Burman also reported on the results with cardiac operation with and without extracorporal circulation. He stated: ". . . It is far safer to digitalize a patient unhurriedly four or five days before surgery . . . than to do so haphazardly in the face of impending disaster." In summary he stated: "Each group was divided into two categories, those who received preoperative digitalization and those who did not. The subsequent course of each group was compared and found to be strikingly dissimilar in favor of those receiving preoperative digitalis."

The general surgery patient

Brockner and Christiansen,[33] in 1965, reported on 235 patients who had surgical operation for malignant disease of the stomach. In some of the patients arrhythmias and heart failure which required digitalization developed in the postoperative period. Of the group with no pre-existing cardiac disease, 4 percent required digitalization after the operation. Of the group with cardiac disease but not in heart failure preoperatively, 50 percent required digitalization after the operation. The authors stated: "The conclusion is drawn that digitalis should be administered before major operations if one or more of the following abnormalities is present: (1) a history of cardiac symptoms; (2) electrocardiographic changes suggestive of myocardial degeneration; (3) enlargement of the heart demonstrated by roentgen examination of the thorax."

McCord,[34] in 1967, did a retrospective study of 186 patients over 60 years of age who had partial colectomy. Sixty-eight of them were found to have coexistent cardiovascular disease. Thirty-nine of the patients with coexistent cardiovascular disease were not digitalized. The morbidity rate for this group was 46 percent and the mortality rate was 18 percent. Twenty-nine patients were digitalized preoperatively. The morbidity in this group was 17 percent and the mortality was 7 percent. McCord summarized his results: "The findings in this study suggest that each elderly patient who is to have a major surgical procedure should be evaluated for the presence of cardiovascular disease. If evidence of such disease is found, the morbidity and mortality from postoperative cardiovascular complications can be reduced by the use of prophylactic digitalization."

Effect of Digitalis in Shock

Data have been accumulating that reveal digitalis is of benefit in hypotension resulting from trauma, hemorrhage, infection, anoxia, and anesthesia.

Keyl and North,[35] in 1957, found that pretreatment of rats with digitalis was effective in lowering the mortality rate from traumatic shock produced by tumbling.

Crowell and Smith,[36] in 1964, bled 100 dogs to shock levels and measured the oxygen deficit developed by the shock as an assessment of the degree of shock. The blood that had been withdrawn was reinfused after the pre-determined oxygen deficit was produced and half of the animals were then digitalized. At an oxygen deficit of 140 ml per kg, all the digitalized animals survived and all the undigitalized died.

Baxter et al,[37] in 1966, demonstrated a myocardial depressant factor in the blood of dogs that had received a 50 percent skin burn 24 hours before cross circulation with normal dogs. The blood of the burned animals produced a 53 percent fall of cardiac output in the normal animals within five minutes after the start of perfusion. These animals were not treated to assess the effect of digitalis on the fall of cardiac output. However, Brand and Lefer,[38] in 1967, found a myocardial depressant factor produced in the blood of cats by hemorrhagic shock. They were able to completely counteract this factor with digitalis. They used the cat papillary muscle as the test device.

Levin and Painter,[39] in 1966, reporting on 28 soldiers (ages 17 to 24 years) treated for meningococcal disease, noted that ten had hypotension which responded in most instances to digitalis. They summarized: "Previous emphasis on peripheral vascular collapse in the etiology of shock in this disease has been at least partially misplaced. A primary decrease in cardiac output appeared to be a major factor in the hypotension seen in the majority of cases in this series. Recommended management of hypotension includes placement of a central venous catheter with continuous monitoring of central venous pressure, intravenous administration of a rapidly acting digitalis preparation in full digitalizing dosage with electrocardiographic monitoring, and use of a continuous isoproterenol infusion to maintain cardiac output in those patients not showing adequate response to digitalis alone."

Hernandez et al,[40] in 1968, used excised atrial muscle of non-failing human hearts as test systems. In 11 cases the heart had not been digitalized and in 15 it had been digitalized before the atrial strips were excised. The muscle strips were preoxygenated for one hour, rendered hypoxic for one hour, and then aerated for one hour. Measurement of the contraction response was recorded throughout. Following anoxia, the undigitalized strips recovered 30 percent of the equilibration contraction level, but the predigitalized strips recovered 62 percent of the equilibration level.

Goldberg et al,[41] in 1962, found that halothane caused a progressive arterial hypotension and decrease of the contractile force of the dog heart with deepening anesthesia. A concentration of 0.2 percent halothane depressed the contractile force by 33 percent, 1 percent halothane depressed the contractile force 73 percent, and 2 percent halothane depressed the contractile force 80 percent. They did the same studies after digitalization and summarized: "Pretreatment with digoxin significantly diminished the negative inotropic and hypotensive effects of 1 and 2 percent halothane anesthesia."

Digitalis Protects in Coronary Occlusion

Cronin and Zoster,[42] in 1965, produced cardiogenic shock in 23 dogs by coronary embolization and then digitalized some of the animals. They summarized their results: "Rapid digitalization . . . caused a substantial elevation in arterial blood pressure and cardiac output in every animal. . . . This restoration of the shocked animals' hemodynamic status toward normal was associated with a marked increase in left ventricular work in all dogs and an average lowering of the end-diastolic left ventricular pressure. . . ."

Marano et al,[43] in 1966, used a comparable technique of coronary embolization in 28 dogs to produce cardiogenic shock. Ouabain produced a significant rise of cardiac output, central aortic pressure and dp/dt in ten of eleven animals. They summarized their findings: "It is concluded that rapid digitalization may be of definite, though transitory, benefit in improving cardiac output and aortic pressure in acute myocardial infarction with shock, even in the absence of hemodynamic evidence of congestive heart failure."

Aldinger,[44] in 1967, prophylactically digitalized 24 dogs and then occluded the artery to the left ventricle. Ventricular fibrillation occurred in 63

percent of the non-digitalized dogs but fibrillation occurred in only 25 percent of the predigitalized dogs. In addition, he stated: "The digitalized animals developed and maintained more myocardial tension than the untreated group when subjected to the stress of acute coronary occlusion."

Malmborg,[45] in 1965, reported on a study of 38 men, aged 40 to 58, who had symptoms of coronary insufficiency but were not in apparent heart failure. He stated: "The results indicate that even at rest acute digitalization had a small but significant effect on both the flow and the intracardiac pressures. During exercise the effect was more marked as evidenced by a highly significant lowering of the heart rate." His data show that some patients were in occult failure at rest and others went into failure with exercise, and digitalis aided both these groups. He summarized: "A beneficial effect of digitalis upon the hemodynamics could be demonstrated in 57 percent and on the subjective symptoms in 53 percent of the studied cases. . . . The present results prove that digitalis therapy was actually of value in the therapy of a certain number of patients with coronary heart disease even when clinical signs of congestive failure were lacking."

Discussion

These data show that small doses of digitalis increase the contractile force of the heart and larger doses produce an even greater increase in the contractile force. Also these data show that digitalis is beneficial to patients who have heart disease but are not in frank heart failure.

A very important clinical application of these ideas is the prophylactic digitalization of patients with cardiac disease who are not in heart failure and are to have an operation. These data show that such patients who are digitalized have a lower incidence of morbidity and mortality than the patients with cardiac disease who are not digitalized preoperatively.

Heilbrunn and Hardin[30] expressed belief that all patients over the age of 70 should be digitalized preoperatively if they are to have thoracotomy. Their patients over 70 years of age who had preoperative digitalization had a decidedly lower incidence of cardiac arrhythmia and mortality therefrom than did those who were not digitalized preoperatively. Burman[32] also found a pronounced lowering of cardiac complications and mortality therefrom in patients with thoracotomy who were completely digitalized before operation. In addition, he pointed out the desirability of slowly digitalizing the patients preoperatively rather than hurriedly doing so when the cardiac complications occurred. Brockner and Christiansen[33] found that patients who were not in heart failure and were operated on for malignant disease of the stomach were 12 times as likely to need postoperative digitalization if they had a history of cardiac symptoms, or had electrocardiographic changes suggestive of myocardial degeneration, or enlargement of the heart as seen roentgenographically. In addition, these observers recommended preoperative digitalization if one or more of these findings were present even though the patient had no sign of heart failure. McCord[34] found that patients over 60 years of age who had cardiovascular disease and underwent partial colectomy had morbidity and mortality rates halved by preoperative digitalization. He considered the patients to have cardiovascular disease if there were positive findings in two of four items of examination: history, physical examination, roentgenogram and electrocardiogram. An isolated finding of electrocardiographic evidence of an old myocardial infarction also established a diagnosis of cardiovascular disease.

The stresses that the patients are subjected to during operation are many. Some that are particularly detrimental to the cardiovascular system are the diminution of tissue perfusion resulting from blood loss, the hypoxia that results from diminished respiration, and the depression of the myocardium resulting from the action of the anesthetic drugs. These stresses are partly responsible for the high incidence of morbidity and mortality that occurs during and after operation in patients who have preexisting cardiovascular disease. Even with the best of management these stresses occur all too frequently. It is possible to lower the incidence of morbidity and mortality following operation by preoperative digitalization of patients who have evidence of cardiovascular disease.

Another clinical application of some of the above summarized data is in the patient with chronic hypertension. In such a patient a constant increase in work load is put on the heart, which may eventually result in myocardial hypertrophy. Digitalis, by increasing the contractile force of the heart, can reduce hypertrophy and failure when chronic stress is put on the heart, as was demonstrated by Cloetta[25] and Williams and Braunwald.[26] These investigators stressed the hearts of

animals by avulsing one aortic valve leaf in one series and constricting the abdominal aorta in the other series. Digitalis limited the resultant myocardial hypertrophy and reduced the mortality from heart failure. The same physiological principles should apply to the stress of chronic hypertension in humans. Therefore, hypertensive patients should have longer lives and less disability when maintained on digitalis.

Reindell and Konig[21] showed that the function of the heart is diminished in patients who have had myocardial infarction and apparently have recovered. These investigators also found that digitalis was effective in returning the function of hearts damaged by myocardial infarcts back to a near normal level. Another observer, Malmborg,[45] found that digitalis had a beneficial effect on the hemodynamics and subjective symptoms of patients with coronary insufficiency. Apparently the increase of contractile force produced by digitalis causes a better perfusion of the ischemic heart as well as the heart damaged by a myocardial infarct.[42-45] Digitalis is of benefit when given to the patient who has angina, an acute myocardial infarction[46] or a healed myocardial infarct, even when the heart is not in failure.

Toxicity is the major deterrent to the use of digitalis. It is known that arrhythmias produced by digitalis can be lethal to the patient with heart failure, particularly when a low level of potassium is present in the blood.[47] Also, it has been shown in animal studies that a dose of digitalis that produces an arrhythmia can decrease the flow of blood in the coronary artery.[48] Therefore, the dose of digitalis should be kept below the arrhythmic dose. It is imperative that the dose of digitalis be individualized for each patient. The "digitalizing dose" has been assessed as 60 percent of the toxic dose.[49,50] However, it is now recognized that even small doses of digitalis have a positive inotropic effect on the heart and produce an increase in the contractile force. Therefore, it is possible to get a beneficial effect from digitalis in a dose much lower than that which was considered a digitalizing dose in the past. When the maximum effect of digitalis is desired, the dose can be raised slowly, preferably over days, until toxicity occurs and then a slightly lower dose can be administered. Nausea, vomiting, yellow vision or scotomata will occur frequently as a symptom of toxicity before arrhythmias occur. However, the pulse must be checked for ectopic beats, bigeminy and runs of tachycardia, and the electrocardiogram can be watched for prolongation of the PR interval or for frank A-V dissociation. Many patients do not have gastrointestinal or nervous system changes before arrhythmias.

A "full digitalizing dose" may become a toxic dose if a patient goes into failure. Olson et al,[51] in 1955, reported a study which showed that in dogs with heart failure ventricular tachycardia developed with one-third the dose of cardioactive drug that was needed to produce the same degree of toxicity in normal dogs. These investigators did not report the blood level of potassium in the animals studied.

Other situations besides decompensation that make the heart more sensitive to digitalis are low level of serum potassium, high level of calcium, hypoxia, oliguria, acute myocardial infarction, and individual variation.[52-59]

The idea that a "full digitalizing dose" must be given to produce a beneficial effect on the heart presupposes that the only effect of digitalis is the slowing of the rate of the heart in failure and arrhythmias. It is now known that the increase in contractile force is the primary beneficial effect of digitalis and the slowing of response of the ventricle in atrial fibrillation and flutter is one of the lesser effects. Even small doses of digitalis produce an increase of contractile force, whereas much larger doses are required to achieve a ventricular slowing in atrial fibrillation.[60] The administration of doses of digitalis smaller than those required to slow the ventricle in atrial fibrillation are effective in improving the function of the heart. The smaller doses of digitalis should not be considered as homeopathic doses.

REFERENCES

1. Starr, I.: The evolution of clinical pharmacology during one lifetime, with discussion of new methods applicable to some of its problems, J. New Drugs, 6:253, 1966.

2. Walton, R. P., Leary, J. S., and Jones, H. P.: Comparative increase in ventricular contractile force produced by several cardiac glycosides, J. Pharmacol. Exp. Ther., 98:346, 1950.

3. Williams, J. F., Klocke, F. J., and Braunwald, E.: Studies on digitalis XIII. A comparison of the effects of potassium on the inotropic and arrhythmia-producing actions of ouabain, J. Clin. Invest., 45:346, 1966.

4. Weissler, A. M., Kamen, A. R., Bornstein, R. S., Schoenfeld, C. D., and Cohen, S.: The effect of deslanoside on the duration of the phases of ventricular systole in man, Amer. J. Cardiol., 15:153, Feb. 1965.

5. Lagerlof, H., and Werko, L.: Studies on the circulation in man, Acta. Cardiol., 4:1, 1949.

6. Malmcrona, R., Schroder, G., and Werko, L.: Haemodynamic effects of digitalis in acute myocardial infarction, Acta. Med. Scand., 180:55, July-Dec. 1966.

7. Bloomfield, R. A., Rapoport, B., Milnor, J. P., Long, W. K., Mebane, J. G., and Ellis, L. B.: Effects of cardiac glycosides upon dynamics of circulation in congestive heart failure; ouabain, J. Clin. Invest., 27:588, 1948.

8. Rodman, T., Gorczyco, C. A., and Pastor, B. H.: The effect of digitalis on the cardiac output of the normal heart at rest and during exercise, Ann. Intern. Med., 55:620, 1961.

9. Mason, D. T.: The cardiovascular effects of digitalis in normal man, Clin. Pharmacol. Therap., 7:1, 1966.

10. Cotten, M. deV., and Stopp, P. E.: Action of digitalis on the non-failing heart of the dog, Amer. J. Physiol., 192:114, 1958.

11. Stewart, H. J., Crane, N. E., Dietrick, J. E., and Thompson, W. P.: Action of digitalis in compensated heart disease, Arch. Intern. Med., 62:547, 1938.

12. Sokolow, M., Weinberg, H. B., Plaut, J. L., and Katz, L. N.: Digitalis in the prevention of recurrent cardiac failure in patients with sinus rhythm, Ann. Intern. Med., 16:427, 1942.

13. Erickson, E. W., and Fahr, G. E.: The effect of Lanatoside-C upon the physiologic state of organically diseased hearts before symptoms and signs of heart failure appear, Amer. Heart J., 29:348, 1945.

14. Hedlund, S.: Klinische untersuchungen mit cedilanid, Cardiologia, Supplementum Ad. Vol. XX (1952), page 44.

15. Braunwald, E., Bloodwell, R. D., Goldberg, L. I., and Morrow, A. G.: Studies on digitalis. I. Observations in man on the effects of digitalis preparations on the contractility of the non-failing heart and on total vascular resistance, J. Clin. Invest., 40:52, 1961.

16. Selzer, A., and Malmborg, R. O.: Hemodynamic effects of digoxin in latent cardiac failure, Circulation, 25:695, 1962.

17. Kahler, R. L., Thompson, R. H., Buskirk, E. R., Frye, R. L., and Braunwald, E.: Studies on digitalis. VI. Reduction of the oxygen debt after exercise with digoxin in cardiac patients without heart failure, Circulation, 27:397, 1963.

18. Mason, D. T., and Braunwald, E.: Studies on digitalis. IX. Effects of ouabain on the non-failing human heart, J. Clin. Invest., 42: 1105, 1963.

19. Murphy, G. W., Schreiner, B. F., Bleakley, P. L., and Yu, P. N.: Left ventricular performance following digitalization in patients with and without heart failure, Circulation, 30:358, 1964.

20. Sonnenblick, E. H., Williams, J. F., Glick, F., Mason, D. T., and Braunwald, E.: Studies of digitalis. XV. Effects of cardiac glycosides on myocardial force-velocity relations in the non-failing human heart, Circulation, 34:532, 1966.

21. Reindell, H., and Konig, K.: Concerning early and maintenance digitalization of the heart, Medico, 4:11, 1967.

22. Mason, D. T.: Clinical significance of recent advances in the pharmacology of cardiovascular drugs, Conn. Med., 32:183, 1968.

23. Selzer, A., Lee, R. H., Goggans, W. H., and Gerbode, F.: The effect of ouabain upon the maximum performance of the normal dog heart, Stanf. Med. Bull., II, No. 4:253, Nov. 1953.

24. Cloetta, M.: Über den einflus der chronischen digitalisbehandlung auf das normale und pathologische herz, Arch. Exp. Path. Pharmak., 59:209, 1908.

25. Cloetta, M.: The biochemical action of digitalis, JAMA, 93: 1462, 1929.

26. Williams, J. F., and Braunwald, E.: Studies on digitalis. XI. Effects of digitoxin on the development of cardiac hypertrophy in the rat subjected to aortic constriction, Amer. J. Cardiol., 16:534, 1965.

27. Heller, M. L., Watson, T. R., and Imredy, D. S.: Postoperative hypoxemia and its treatment with nasal oxygen: polarographic study, Surgery, 58:819, 1965.

28. Brown, J. M.: Anesthesia and contractile force of the heart: a review, Anesth. Analg. (Cleveland), 39:487, 1960.

29. Wheat, M. W., and Burford, T. H.: Digitalis in surgery: extension of classical indications, J. Thorc. Cardiov. Surg., 41:102, 1961.

30. Heilbrunn, A., and Hardin, C. A.: Thoracotomy in patients over the age of seventy, J. Thorac. Cardiov. Surg., 46:13, 1963.

31. Bergh, N. P., Dottori, O., and Malmberg, R.: Prophylactic digitalis in thoracic surgery, Scand. J. Resp. Dis., 48:197, 1967.

32. Burman, S. O.: Digitalis and thoracic surgery, J. Thorac. Cardiov. Surg., 50:873, Dec. 1965.

33. Brockner, J., and Christiansen, J.: Evaluation of surgical patients for preoperative digitalisation, Acta Chir. Scand., 129:1, 1965.

34. McCord, B. L.: The digitalization of elderly patients with cardiovascular disease requiring colectomy, J. Kansas Med. Soc., 68:295, 1967.

35. Keyl, A. C., and North W. C.: Cardiac glycosides in traumatic shock, J. Pharmacol. Exper. Ther., 119:229, 1957.

36. Crowell, J. W., and Smith, E. C.: Oxygen deficit and irreversible hemorrhagic shock, Amer. J. Physiol., 206:313, 1964.

37. Baxter, C. R., Cook, W. A., and Shires, G. T.: Serum myocardial depressant factor of burn shock, Surg. Forum, 17:1, 1966.

38. Brand, E. D., and Lefer, A. M.: Influence of positive inotropic agents on the action of myocardial depressant factor in the plasma of cats in postoligemic shock, Proc. Soc. Exp. Biol. Med., 126:335, 1967.

39. Levin, S., and Painter, M. B.: The treatment of acute meningococcal infection in adults, a reappraisal, Ann. Intern. Med., 64:1049, 1966.

40. Hernandez, A., Goldring, D., and Burton, R. M.: Prophylactic digitalization, Amer. J. Dis. Child., 115:576, 1968.

41. Goldberg, A. H., Maling, H. M., and Gaffney, T. E.: The value of prophylactic digitalization in halothane anesthesia, Anesthesiology, 23:207, 1962.

42. Cronin, R. F. P., and Zoster, T.: Hemodynamic effects of rapid digitalization in experimental cardiogenic shock, Amer. Heart J., 69:233, 1965.

43. Marano, A. J., Kline, H. J., Cestero, J., and Kuhn, L. A.: Hemodynamic effects of ouabain in experimental acute myocardial infarction with shock, Amer. J. Cardiol., 17:327, 1966.

44. Aldinger, E. E.: Prophylactic digitalization and acute coronary occlusion in dogs, Vasc. Dis., 4:83, 1967.

45. Malmborg, R. O.: A clinical and hemodynamic analysis of factors limiting the cardiac performance in patients with coronary heart disease, Acta Med. Scand. Supp., 426:1, 1965.

46. Mason, D. T.: Personal communication, Mar. 1969.

47. Rodensky, P. L., and Wasserman, F.: Observations on digitalis intoxication, Arch. Intern. Med., 108:171, 1961.

48. Dearing, W. H., Essex, H. E., Herrick, J. F., and Barnes, A. R.: Experiments with calculated therapeutic and toxic doses of digitalis. III. Effects on the coronary blood flow, Amer. Heart J., 25:719, 1943.

49. Rose, O. A., Batterman, R. C., and DeGraff, A.: Clinical studies on digoxin, a purified digitalis glycoside, Amer. Heart J., 24: 435, 1942.

50. DeGraff, A. C., Batterman, R. C., and Rose, O. A.: Digitoxin. Its evaluation for initial digitalization of the patient with congestive heart failure, JAMA, 138:475, 1958.

51. Olson, R. E., Rousch, G., and Liang, M. M.: Effect of acetyl strophanthidin upon the myocardial metabolism and cardiac work of normal dogs and dogs with congestive heart failure, Circulation, 12: 755, 1955.

52. Lown, B.: Digitalis and potassium, Advances Intern. Med., 8: 125, 1956.

53. Gold, H., and Edwards, D. J.: The effects of ouabain on the heart in the presence of hypercalcemia, Amer. Heart J., 3:45, 1927.

54. Baum, G. L., Dick, M. M., Kaupe, A., and Carballo, J.: Factors involved in digitalis sensitivity in chronic pulmonary insufficiency, Amer. Heart J., 57:460, 1959.

55. Doherty, J. E., and Perkins, W. H.: Studies with tritiated digoxin in renal failure, Amer. J. Med., 37:536, 1964.

56. Bellet, S., Johnston, C. G., and Schecter, A.: Effect of cardiac infarction on the tolerance of dogs to digitalis. An experimental study, Arch. Intern. Med., 54:509, 1934.

57. Travell, J., Gold, H., and Modell, W.: Effect of experimental cardiac infarction on response to digitalis, Arch. Intern. Med., 61:184, 1938.

58. Craig, L. C., Lown, B., and Levine, S. A.: Resistance and sensitivity to digitalis, JAMA, 166:2139, 1958.

59. Hall, R. L.: Sensitivity to digitalis, Penn. Med., 69:37, May 1966.

60. Gold, H., Cattell, M., Greiner, T., Hanlon, L. W., Kwit, N. T., Modell, W., Cottone, E., Benton, J., and Otto, H. L.: Clinical pharmacology of digoxin, J. Pharmacol. Exp. Ther., 109:45, Sept. 1953.